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# Vagus Nerve Stimulation Paired With Upper Limb Rehabilitation After Chronic Stroke

## A Blinded Randomized Pilot Study

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**Background and Purpose**—We assessed safety, feasibility, and potential effects of vagus nerve stimulation (VNS) paired with rehabilitation for improving arm function after chronic stroke.

**Methods**—We performed a randomized, multisite, double-blinded, sham-controlled pilot study. All participants were implanted with a VNS device and received 6-week in-clinic rehabilitation followed by a home exercise program. Randomization was to active VNS (n=8) or control VNS (n=9) paired with rehabilitation. Outcomes were assessed at days 1, 30, and 90 post-completion of in-clinic therapy.

**Results**—All participants completed the course of therapy. There were 3 serious adverse events related to surgery. Average FMA-UE scores increased 7.6 with active VNS and 5.3 points with control at day 1 post-in-clinic therapy (difference, 2.3 points; CI, −1.8 to 6.4;  $P=0.20$ ). At day 90, mean scores increased 9.5 points from baseline with active VNS, and the control scores improved by 3.8 (difference, 5.7 points; CI, −1.4 to 11.5;  $P=0.055$ ). The clinically meaningful response rate of FMA-UE at day 90 was 88% with active VNS and 33% with control VNS ( $P<0.05$ ).

**Conclusions**—VNS paired with rehabilitation was acceptably safe and feasible in participants with upper limb motor deficit after chronic ischemic stroke. A pivotal study of this therapy is justified.

**Clinical Trial Registration**—URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT02243020. (*Stroke*. 2018;49:2789-2792. DOI: 10.1161/STROKEAHA.118.022279.)

**Key Words:** motor cortex ■ neuromodulation ■ plasticity ■ rehabilitation ■ stroke ■ upper extremity ■ vagus nerve

Impaired use of the upper limb is one of the most common symptoms after stroke, and improving upper limb function is a priority for many patients.<sup>1</sup> Clinical trials of increased dose of upper extremity task-specific training have been disappointing.<sup>2</sup> This suggests new interventions are needed to maximize poststroke motor recovery.<sup>3</sup>

Vagus nerve stimulation (VNS) paired with movement has been shown to drive task-specific plasticity in the motor cortex in rodent models and improve forelimb function after experimental stroke.<sup>4</sup> In our first-in-human, randomized, controlled, open clinical trial, VNS paired with upper limb rehabilitation was safe and feasible in people with upper limb deficit at least 6 months after ischemic stroke.<sup>5</sup>

The purpose of this pilot study was to further assess safety, feasibility, and efficacy of VNS paired with upper limb

rehabilitation in chronic ischemic stroke, with blinded, sham VNS control.

### Methods

This article adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines. Requests for data will be considered by the corresponding author after Food and Drug Administration postmarket approval.

This was a randomized, sham stimulation controlled, and fully blinded study of VNS paired with rehabilitation in people with arm weakness after ischemic stroke. Participants in both groups were implanted with the VNS device. Participants, therapists, and outcome assessors were blinded to group allocation.

The study was approved by an institutional review board at each institution and subject to appropriate regulatory approvals (Food and Drug Administration investigational device exemption No. 130287 and UK Medicines and Healthcare Products Regulatory Agency [MHRA]

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**The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.118.022279>.**

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No. CI/2015/0011). It was registered on <http://www.clinicaltrials.gov> (NCT02243020). Written informed consent was obtained in compliance with the requirements set forth in US Food and Drug Administration, Code of Federal Regulations Title 21. The study was conducted according to the Declaration of Helsinki.

## Participants

Enrollment at the 4 sites is shown in Table I in the [online-only Data Supplement](#). People with a history of unilateral supratentorial ischemic stroke that occurred between 4 months to 5 years before randomization, aged  $\geq 30$  and  $\leq 80$  years, and with an FMA-UE between 20 to 50 were eligible for inclusion (Table II in the [online-only Data Supplement](#)).

## Protocol Summary

A presurgery assessment was performed. After VNS implantation and  $\approx 1$  week of recovery, participants were randomized to either active VNS (0.8 mA) or control VNS (0.0 mA), and baseline assessments were repeated. In-clinic rehabilitation therapy began on the next day and was delivered  $\approx 3\times$  a week for 6 weeks (18 visits; Figure I in the [online-only Data Supplement](#)). Outcomes assessments were performed on days 1, 7, 30, and 90 after completion of in-clinic therapy.

After 6 weeks of in-clinic therapy, all participants began daily, therapist-prescribed home exercises. For the first 30 days of at-home therapy, all participants received 0 mA VNS. Thereafter, participants received VNS according to their randomized allocation. After the

day-90 assessment, the control VNS group crossed over to receive 6 weeks of in-clinic rehabilitation paired with active VNS (0.8 mA) followed by outcome assessments at days 1, 7, 30, and 90 thereafter.

Further details on methodology are given in Appendix in the [online-only Data Supplement](#).

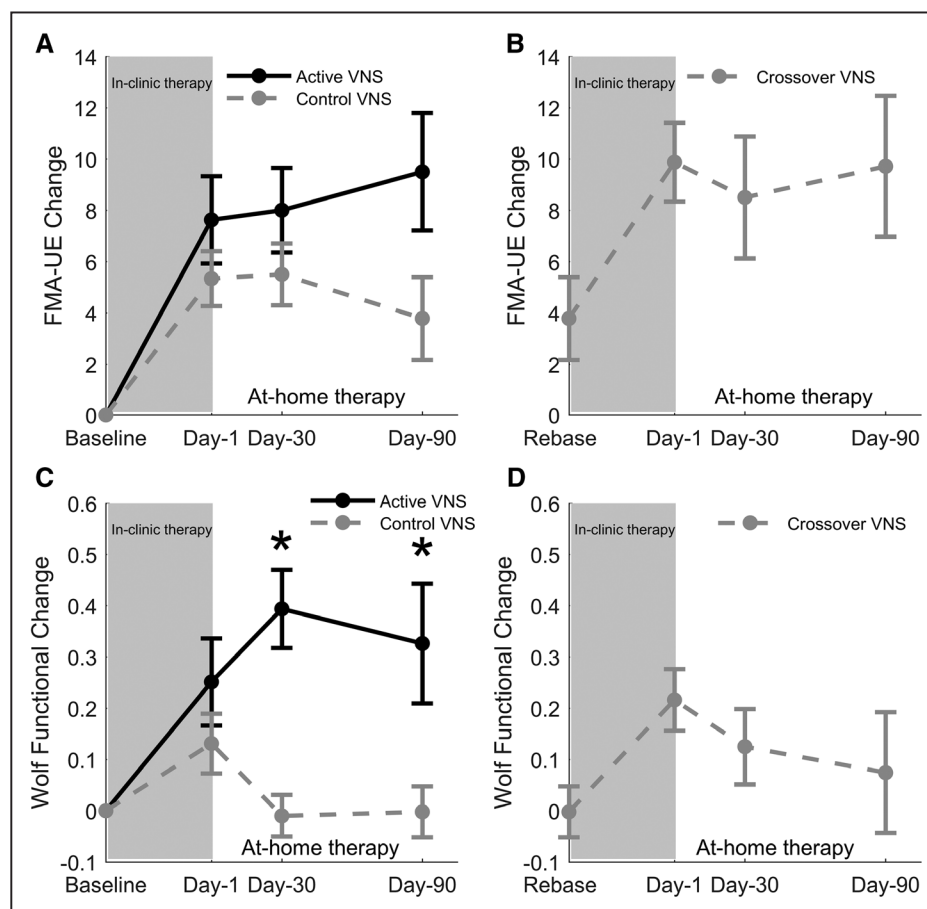
## Main Study Outcome Measures

The main safety outcome measure was the number of serious adverse events related to the device or therapy. The main feasibility measure was the number of participants who completed the minimum number of visits during the randomized portion of the study (at least 12 therapy visits).

Efficacy outcomes included the FMA-UE,<sup>6</sup> Wolf Motor Function Test (WMFT; time and functional), Box and Block Test, Nine-Hole Peg Test, Stroke Impact Scale, and Motor Activity Log. Because this was a pilot study, no primary or secondary efficacy measures were designated.

## Sample Size and Statistical Analysis

No formal sample size calculation was performed for this pilot study. Efficacy analyses were performed on the intention-to-treat population and included all randomized participants. Missing data were not imputed. The change in outcome measures at each time point was compared between groups using 2-tailed, unpaired *t* tests. Fisher exact test was used to calculate the significance for response rates. For all comparisons,  $\alpha$  was set at 0.05.



**Figure 1.** Fugl-Meyer assessment–upper extremity (FMA-UE; mean  $\pm$  SEM) and Wolf Motor Function Test (WMFT) scores (mean  $\pm$  SEM). **A**, Change in FMA-UE score during blinded follow-up for active vagus nerve stimulation (VNS) and controls from baseline and 3 posttreatment assessments. **B**, Change in FMA-UE score following crossover to active VNS. **C**, Change in WMFT functional score during blinded follow-up for active VNS and controls. **D**, Change in WMFT score following crossover to active VNS. Shaded area indicates the 6 wk of in-clinic therapy. Rebase, baseline in controls before starting active VNS. Days 1 to 30 (after in-clinic therapy) consisted of at-home therapy with no VNS for both groups. From days 30 to 90, active VNS group received VNS (0.8 mA) and controls received control VNS (0 mA) with at-home therapy. \* $P=0.029$  at post-90 d and  $P<0.001$  at post-30 d.

**Table. Change in Outcome Measures (Intention-to-Treat Analysis, n=17 [Active VNS, 8; Control, 9])**

Measure	Day-1 Difference Post-In-Clinic Therapy*		Day-90 Difference Post-In-Clinic Therapy*	
	95% CI	P Value	95% CI	P Value
FMA-UE	2.29 (−1.9 to 6.47)	0.2604	5.72 (−0.15 to 11.6)	0.055
WMFT functional	0.12 (−0.10 to 0.33)	0.2625	0.33 (0.04 to 0.61)	0.029
WMFT time, s	−3.02 (−11 to 5.24)	0.4215	−4.04 (−14 to 5.64)	0.362
Stroke Impact Scale (hand)	5.66 (−11 to 22.7)	0.4889	2.71 (−14 to 19.9)	0.741
Box and Block Test	−2.93 (−6.3 to 0.44)	0.0835	−0.23 (−4.1 to 3.66)	0.903
Nine-Hole Peg Test	−2.25 (−58 to 53.5)	0.9245	−9.18 (−48 to 29.2)	0.580
Motor Activity Log	NA	NA	17.93 (−0.37 to 36.2)	0.054

FMA-UE indicates Fugl-Meyer assessment–upper extremity; NA, not applicable; VNS, vagus nerve stimulation; and WMFT, Wolf Motor Function Test.

\*Difference between groups: active VNS - control VNS.

## Results

Twenty-two people consented to participate in the study. Of these, 17 participants were implanted and randomized (8 to active VNS and 9 to control; Figure II in the [online-only Data Supplement](#)). All participants completed the randomized portion of the study. Baseline characteristics of participants are shown in Table III in the [online-only Data Supplement](#). Details on protocol adherence, feasibility, and blinding are provided in the [online-only Data Supplement](#).

## Safety

There were 3 serious adverse events related to implantation surgery, including 1 implantation wound infection requiring treatment with intravenous antibiotics but resolved; 1 case of shortness of breath and dysphagia, likely because of intubation, which recovered; and 1 case of hoarseness because of vocal cord palsy. There were no serious adverse events reported as associated with stimulation. Full details of adverse events are shown in Appendix in the [online-only Data Supplement](#).

## Efficacy

Between-group differences in FMA-UE are shown in Figure 1 and the Table. At day 90, the response rate (defined as FMA-UE change  $\geq 6$  points<sup>7</sup>) was 88% in the active group and 33% in control ( $P=0.03$ ; Figure 2). Between-group differences in Wolf Motor Function Test are shown in Figure 1 and the Table.

After crossover to active VNS in controls, FMA-UE scores increased to 9.8 points above baseline at day 1 after in-clinic therapy ( $P<0.001$ ) and by 9.7 points at day 90 ( $P=0.01$ ; Figure 1). Response rates were 88% and 57% at these time points, respectively (Figure 2). Wolf Motor Function Test data are shown in Figure 1. Full details on all outcome measures are shown in Tables V and VI in the [online-only Data Supplement](#).

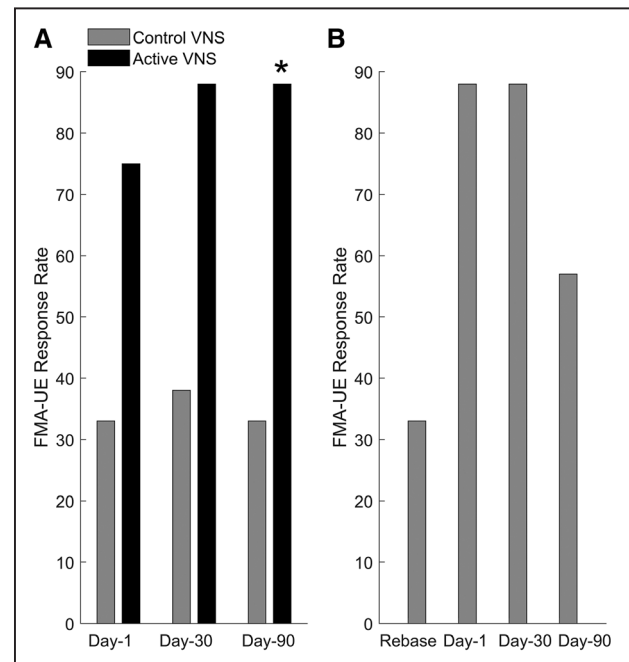
## Discussion

The primary objective of this pilot study was to assess the safety and feasibility of using paired VNS to improve arm function after chronic ischemic stroke. We found this technique to be feasible, including the use of home-based VNS,

and demonstrated safety in-line with that expected for VNS devices. The study was not powered to assess efficacy, although there were significant differences between groups in some measures at day 90.

There are several important differences between this and our previous clinical study.<sup>5</sup> This study was fully blinded, all participants were implanted with a VNS device, control participants crossed over to receive the active VNS therapy, and participants continued rehabilitation exercises at home for several months.

There were no significant differences between groups immediately after in-clinic therapy completion, but there was a significant difference by 90 days because of maintained benefit by the VNS group with corresponding decline in the control group and a higher percentage of responders who



**Figure 2.** Average Fugl-Meyer assessment–upper extremity (FMA-UE) response rate. **A**, Responder rate (defined as FMA-UE change  $\geq 6$  from baseline) for the first 90 d in paired vagus nerve stimulation (VNS; black) and controls (gray). **B**, Responder rates after control group crossed over to receive active VNS therapy. Rebase, baseline in controls before starting active VNS therapy. \* $P<0.05$ , Fisher exact test.

achieved a clinically meaningful change for the FMA-UE (change,  $\geq 6$  points) with active VNS treatment.<sup>7</sup> Although we cannot definitively conclude these differences are because of paired active VNS treatment, our findings are consistent with the effect of a neuroplastic treatment where time may be needed for benefit to accrue. It is of note that control participants experienced a benefit similar to the initial VNS participants when they crossed over to active VNS treatment.

This pilot study showed that rehabilitation paired with VNS is an acceptably safe and feasible intervention for the treatment of upper limb weakness after ischemic stroke. The study demonstrated sufficient safety, feasibility, and potential efficacy to support a larger pivotal trial.

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### Disclosures

Drs Dawson, Kimberley, and Prudente have received reimbursement for conference attendance where results of the study were presented from MicroTransponder, Inc. Dr Cramer has served as a consultant for MicroTransponder, Inc, as well as Roche, and Dart Neuroscience. D. Pierce, Dr Engineer, Dr Prudente, and B. Tarver are employees of MicroTransponder, Inc. The other authors report no conflicts.

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